

Draw
Pharmacology *in your mind*

**Autonomic
Nervous
System**

If you are a pharmacy student
If you are postgraduate and want
to revise pharmacology by an
easy way
If you are using any pharmacology
reference

this file will aid you

> And wait for more <

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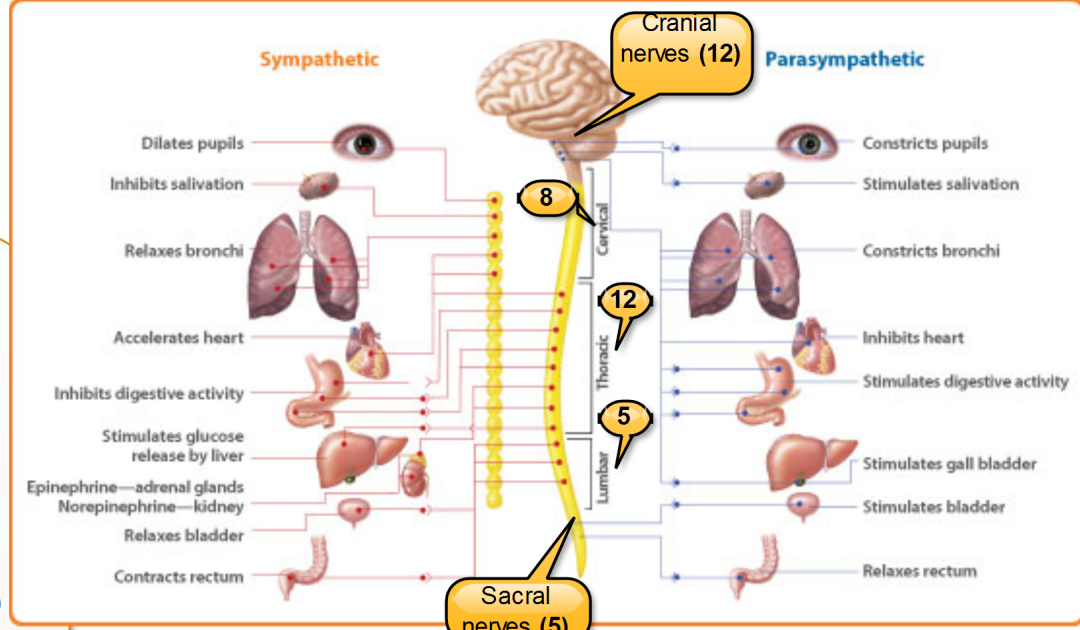
لا تنسوني من صالح دعائكم

Pharmacist. **Alaa Nasr**

د. آلاء نصر

VISIT...

LANZAROTE
Caliente.COM



Central control of ANS

ANS is controlled by higher centers in brain

- 1- Hypothalamus
- 2- Medulla oblongata, and others and also spinal cord

Dual innervation by ANS

→ Most organs are innervated by **both** divisions of ANS "Sympathetic and Parasympathetic" → They work in harmony together → keeping homeostatic balance by their opposite actions on the body

Usually **one system** (sympathetic OR parasympathetic) **predominates** in controlling the activity of the organ **this is called "Autonomic tone"**

ex. Heart and GIT → Parasympathetic predominates

Blood vessels → Sympathetic predominates

Eye → Parasympathetic predominates

Bronchi → Sympathetic predominates

There are certain organs that receive **ONLY sympathetic innervation** !

- 1- Blood vessels
- 2- Sweat glands
- 3- Pilomotor muscle
- 4- Kidney
- 5- Adrenal medulla

Chemical transmission in ANS

Transmission of nerve impulses from
1- one nerve to another or from
2- nerve to effector organ
→ is mediated by chemical mediators
→ called **neurotransmitters**

Main neurotransmitters in ANS

- 1- **Acetylcholine (ACh)** → released by "cholinergic nerves"
 - 2- **Noradrenaline (NA)** → released by "adrenergic nerves"
- And both are called "autonomic nerves"

Functions of ANS

Activated in response to **resting state**

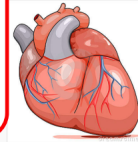
Parasympathetic nervous system

Sympathetic nervous system

Activated in response to **stressful conditions**

Heart

rate ↓
force of contraction ↓
Blood pressure ↓



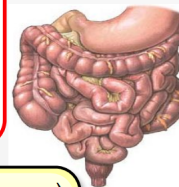
Lungs

Bronchoconstriction



GIT

motility ↑
blood flow ↑
sphincter → relaxation



Vagus (Parasympathetic nerve) predominates → keep GIT in contacted state → stimulate *peristalsis* → "Vagal tone"

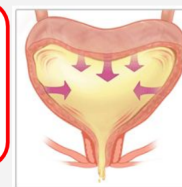
Watery saliva

Eye

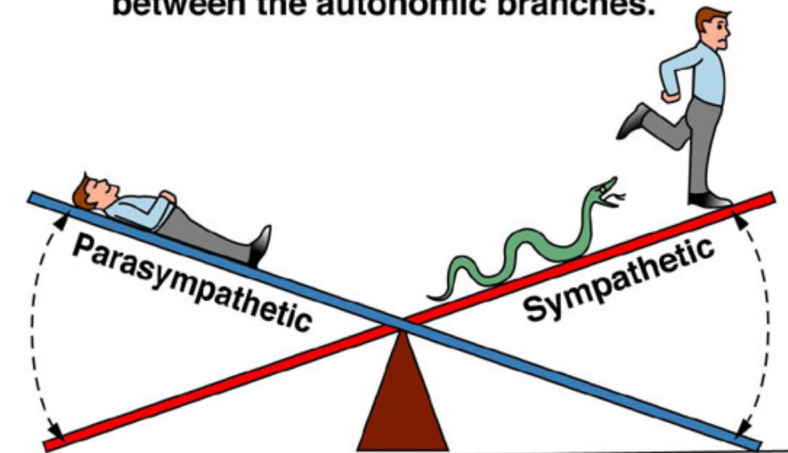
Contraction of circular muscle of iris → accommodation for near vision → Constricted pupil → **Miosis**

Bladder

Urine evacuation
→ Relaxation of sphincter muscle
→ Contraction of detrusor muscle



Homeostasis is a dynamic balance between the autonomic branches.



Rest-and-digest:
Parasympathetic activity dominates.

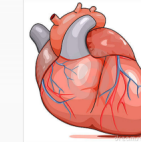
Fight-or-flight:
Sympathetic activity dominates.

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Figure 11-1

Heart

rate ↑
force of contraction ↑
Blood pressure ↑ →
Contracted blood vessels



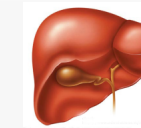
Lungs

Bronchodilatation



Liver

Glycogenolysis
→ ↑ glucose



GIT

motility ↓
blood flow ↓ ,
sphincter will contract



Eye

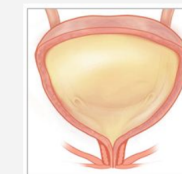
Dilated eye pupil → **Mydriasis**

Skeletal muscle blood flow ↑
(vasodilation of skeletal muscle blood vessels) ,
Glycogenolysis ↑



Bladder

Urine retention
→ Relaxation of detrusor muscle
→ Contraction of sphincter muscle



Dermal blood flow ↓

Viscous, little saliva

Fat

Lipolysis → fatty acid liberation

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Steps involved in neurotransmission

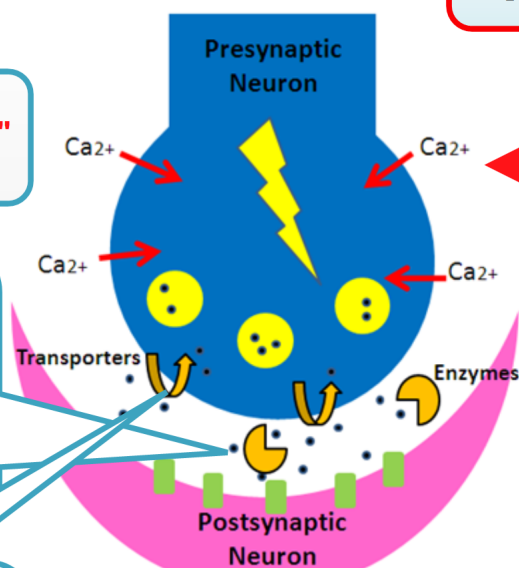
6- Then comes the last step
"Termination of the neurotransmitter response"
 which is done by 2 mechanisms

1- Enzymatic destruction

- 1- **Ach** is hydrolysed / destroyed by cholinesterases → to choline + acetic acid
- 2- **NA** is destroyed by :
 - a) **MAO** (monoamine oxidase) → inside nerve terminal
 - b) and **COMT** (catechol-o-methyl transferase) → outside nerve terminal

2- Reuptake of transmitter by nerve terminal to be stored , re-used

- 1- **NA** → is reuptaken as a whole
- 2- **Ach** → only the choline part is reuptaken to be recombined with the acetate part inside the nerve ending



1- The nerve impulses / action potential move through the nerve as waves of depolarization till reaching the **nerve terminal**

We should notice → There is no direct contact between the nerve terminal and the effector organ so, connection between the is done by chemical neurotransmitters in the synapse

2- Then **influx of Ca^{2+}** ions occurs

3- Vesicles containing neurotransmitter adhere to the synaptic membrane
 → Release of neurotransmitter by exocytosis

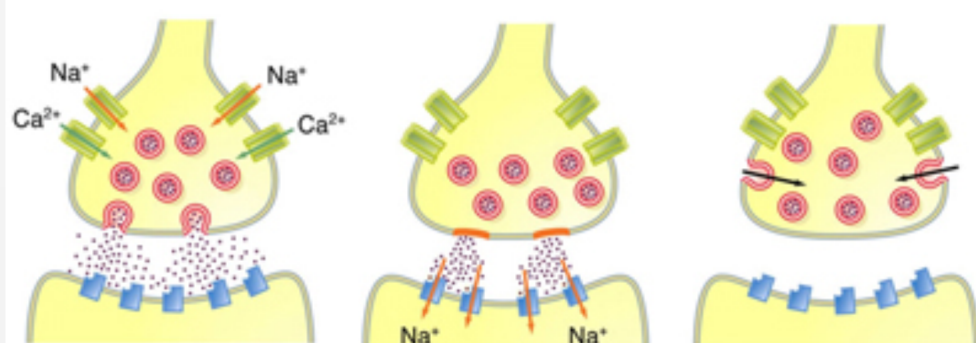
4- The neurotransmitter bind to its **specific receptor** on the effector organ:
 → **Ach** → binds to cholinergic receptors
 → **NA** → binds to adrenergic receptors

5- This leads to changes in the permeability of cell membrane of the effector organs → leads to initiation of a response in the effector organ **according to the type of the neurotransmitter**

If the neurotransmitter is **EXCITATORY** to the organ (ex. Ach in **smooth muscles**)

- Open Na^+ or Ca^{2+} channels
- ↑ Permeability to Na^+ or Ca^{2+} ions
- **influx** (inward diffusion) of Na^+ or Ca^{2+}
- **Depolarization** of cell membrane
- "Excitatory postsynaptic potential (EPSP)"
- **Stimulation** of the effector organ (ex. muscle contraction)

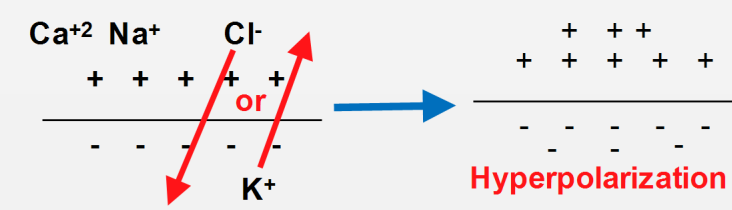
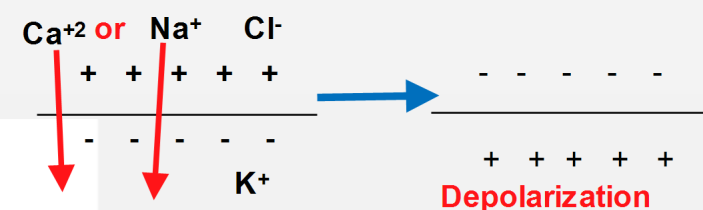
- Open K^+ or Cl^- channels → **influx** (inward diffusion) of Cl^- ions **OR** **Outflux** (outward diffusion) of K^+ ions
- **Hyperpolarization** of cell membrane
- "inhibitory postsynaptic potential (IPSP)" → **inhibition** of the effector organ (ex.bradycardia →decreased heart rate)



① **Transmitter Release**

② **Receptor Activation**

③ **Active Termination**



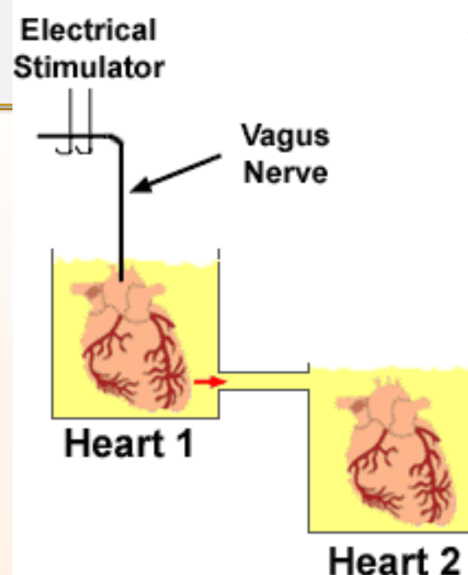
Types of cholinesterases

1- True cholinesterase

- called **Acetylcholinesterase**
- **Can not** degrade any substance except acetylcholine
- Present **only** in CNS and ANS

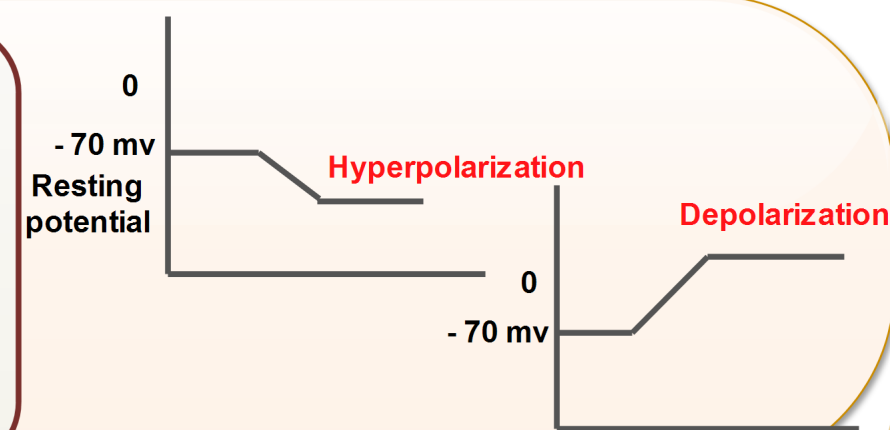
2- Pseudocholinesterase

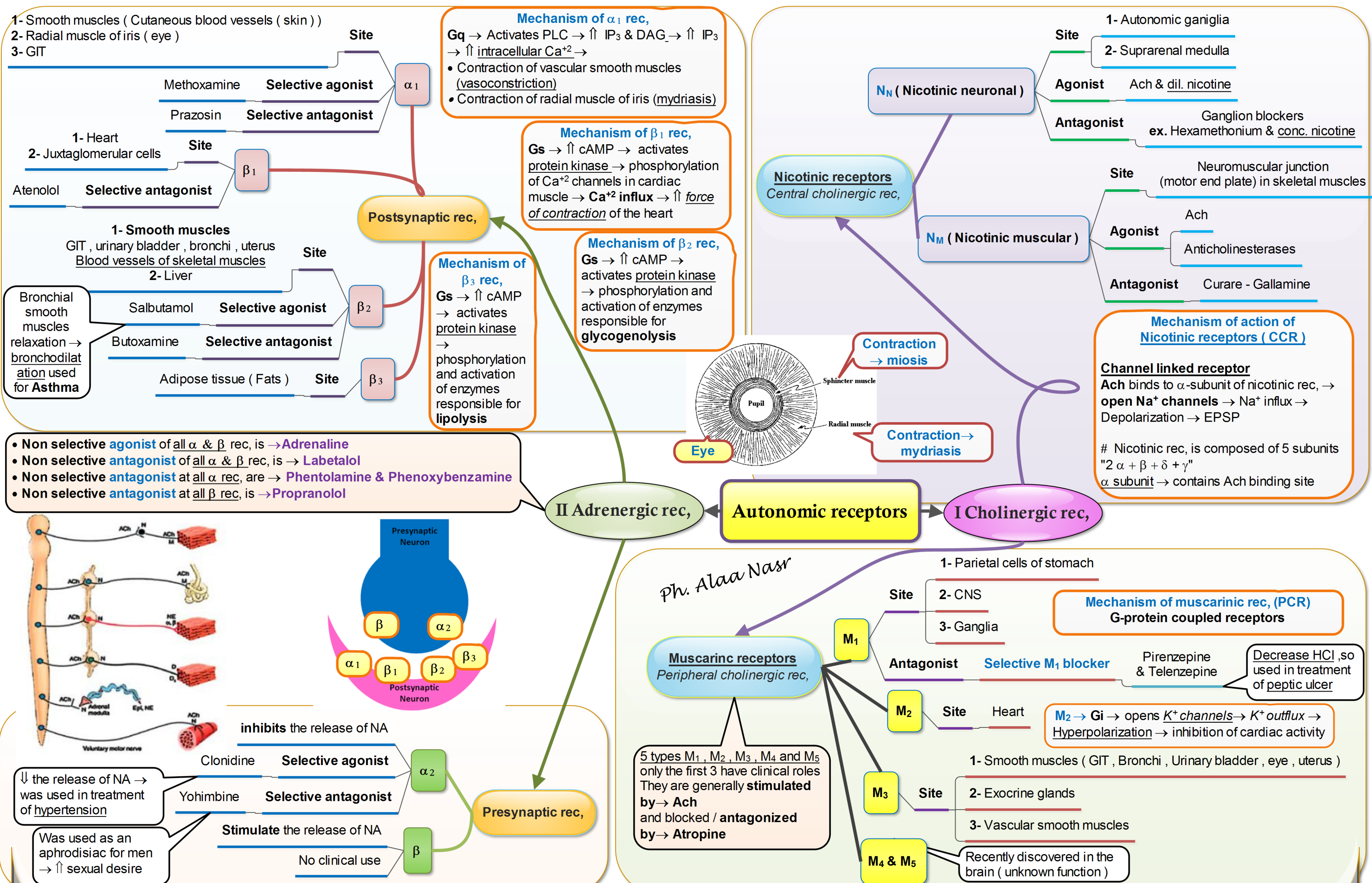
- Can degrade acetylcholine and any substance similar to it such as **succinylcholine** (skeletal muscle relaxant)
- present in other places such as **blood**

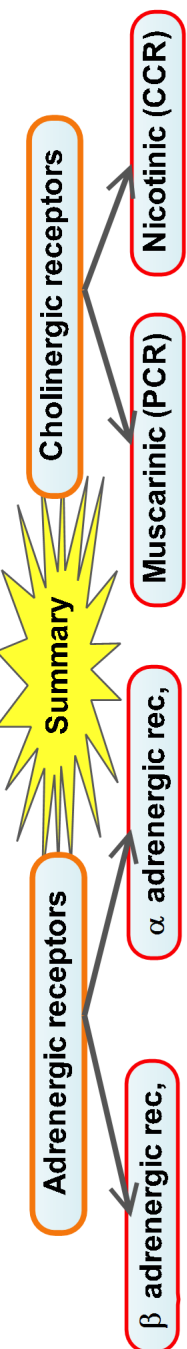


Otto Loewi's experiment

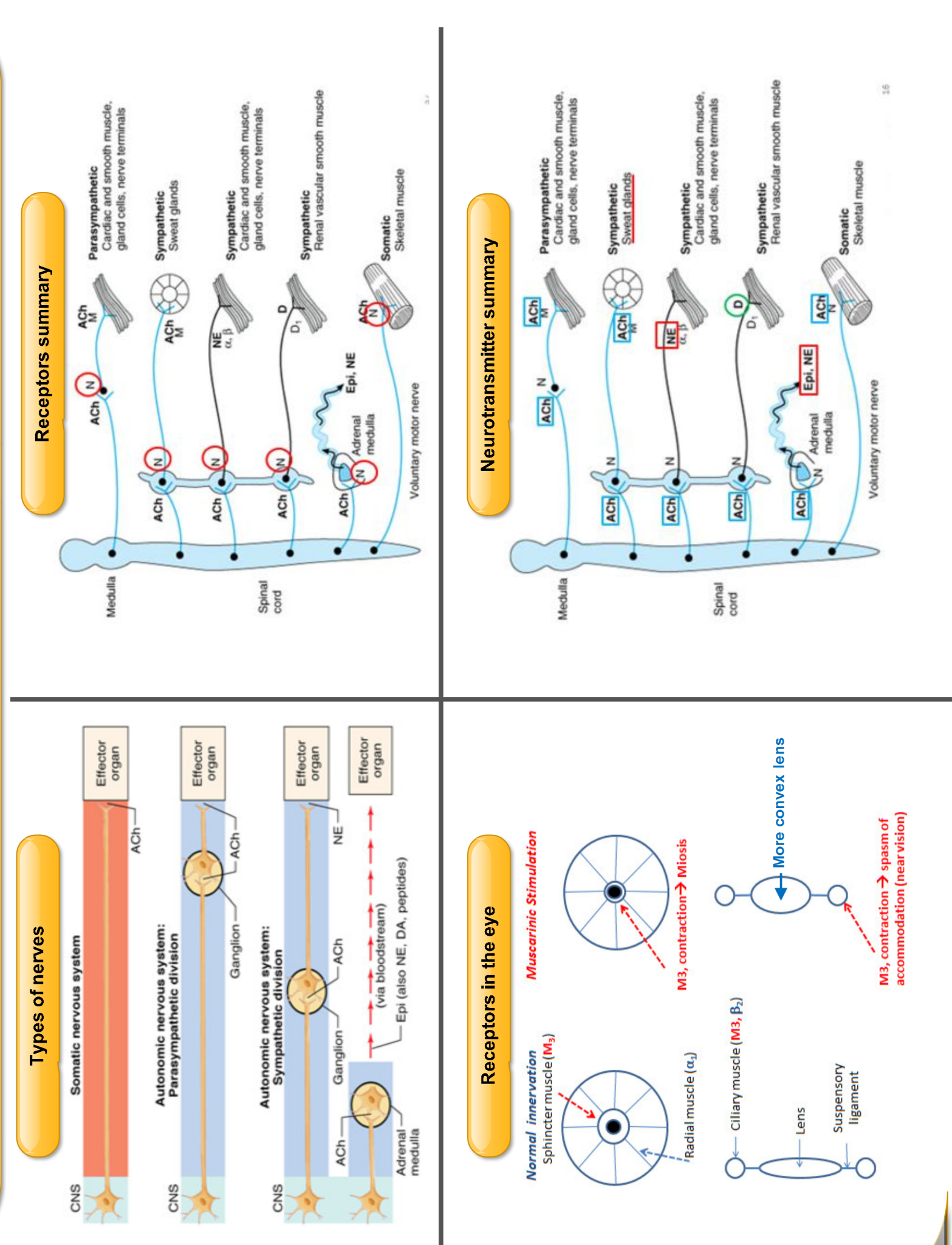
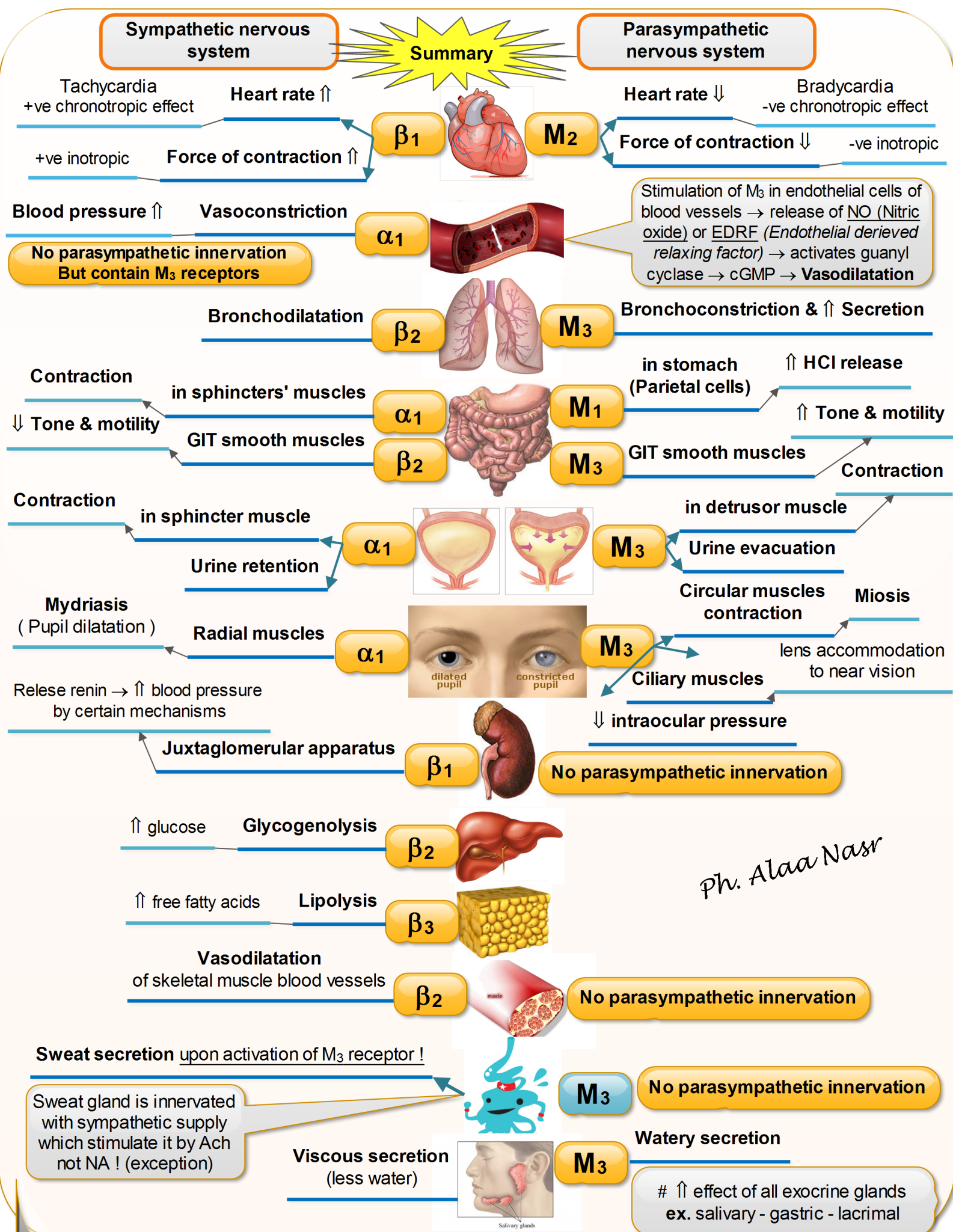
- 2 isolated hearts of 2 frogs in 2 connected containers contain saline solution
- Loewi stimulated the vagus nerve of "Heart 1" caused it to **slow down**
- After a delay he noticed that "Heart 2" also **slowed down**
- That **indicated** that some sort of substance "**neurotransmitter** which we now know as **acetylcholine**" flowed from 1 to 2







Receptor name	Site	mechanism	Agonist	Antagonist
N_N	1- Autonomic ganglia 2- Suprarenal medulla	Channel linked receptor Ach binds to α -subunit of nicotinic rec,	Ach dil. nicotine	Ganglion blockers ex. Hexamethonium conc. nicotine
N_M	Neuromuscular junction (motor end plate) in skeletal muscles	→ open Na ⁺ channels → Na ⁺ influx → Depolarization → EPSP	Ach Anticholinesterases	Neuromuscular blockers ex. curare Gallamine
M₁	1- Parietal cells of stomach 2- CNS 3- Ganglia	Gq → activates <u>phospholipase C</u> → ↑ IP ₃ & DAG	Ach	Atropine (non selective) Pirenzepine & Telenzepine (selective)
M₂	Heart	Gi → opens <u>K⁺ channels</u> → K ⁺ outflux → <u>Hyperpolarization</u> → inhibition of cardiac activity	Ach	Atropine (non selective)
M₃	1- Smooth muscles (GIT , Bronchi , Urinary bladder , eye , uterus) 2- Exocrine glands 3- Vascular smooth muscles	Gq → Activates PLC → ↑ IP ₃ & DAG → ↑ IP ₃ → ↑ intracellular Ca ⁺² → smooth muscles contraction and gland secretion	Ach Muscarine	Atropine (non selective) Oxybutenin (selective)
α₁	1- Smooth muscles ex. Cutaneous blood vessels (skin) 2- Radial muscle of iris (eye) 3- GIT	Gq → Activates PLC → ↑ IP ₃ & DAG → ↑ IP ₃ → ↑ intracellular Ca ⁺² → Contraction of vascular smooth muscles (<u>vasoconstriction</u>) , Contraction of radial muscle of iris (<u>mydriasis</u>)	Adrenaline (non selective) Methoxamine (selective)	Phentolamine & Phenoxybenzamine (non selective) Prazocin (selective)
α₂	Presynaptic	Gi → inhibits adenyl cyclase → ↓ cAMP → ↓ release of NA	Adrenaline (non selective) Clonidine (selective)	Phentolamine & Phenoxybenzamine (non selective) Yohimbine (selective)
β₁	1- Heart 2- juxtaglomerular cells	Gs → ↑ cAMP → activates <u>protein kinase</u> → phosphorylation of Ca ⁺² channels in cardiac muscle → Ca ⁺² influx → ↑ <u>force of contraction</u> of the heart	Adrenaline (non selective) Dobutamin (selective)	Propranolol (non selective) Atenolol (selective)
β₂	1- Smooth muscles GIT , urinary bladder , bronchi , uterus Blood vessels of skeletal muscles 2- Liver	Gs → ↑ cAMP → activates <u>protein kinase</u> → phosphorylation and activation of enzymes responsible for glycogenolysis	Adrenaline (non selective) Salbutamol (selective)	Propranolol (non selective) Butoxamine (selective)
β₃	Adipose tissue (Fats)	Gs → ↑ cAMP → activates <u>protein kinase</u> → phosphorylation and activation of enzymes responsible for lipolysis	Adrenaline (non selective)	Propranolol (non selective)



Concepts of autonomic disorders

Activity of sympathetic or parasympathetic in certain organ may abnormally increase or decrease causing disorders → that can be treated with drugs working on receptors

Example

If parasympathetic activity to GIT abnormally **increase** → extra ↑ in motility of GIT → diarrhea and colics
So, using of a drug that ↓ GIT motility (like atropine) may help in this case

and If parasympathetic activity to GIT abnormally **decrease** → extra ↓ in motility of → Atony / paralytic ileus
So, using of a drug that ↑ GIT motility (like Ach) may help in this case

Autonomic drugs

Parasympathomimetics	Stimulate muscarinic rec,
Parasympatholytics	Block muscarinic rec,
Sympathomimetics	Stimulate α & β rec,
Sympatholytics	Block α & β rec,
Ganglionic stimulants	Stimulate N _N rec,
Ganglionic blockers	Block N _N rec,

Pharmacological action of Acetylcholine

1. Muscarinic actions

- Smooth muscles
- Cardiac muscle
- Exocrine glands

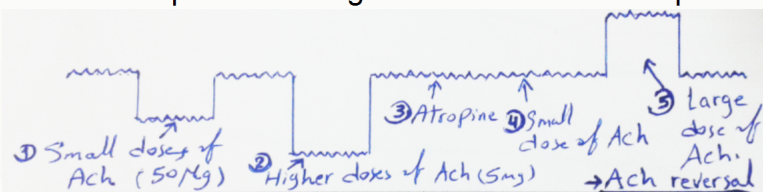


2. Nicotinic actions

- Autonomic ganglia
- Adrenal medulla
- Skeletal muscles (MEP)

A. Effect on autonomic ganglia & adrenal medulla (N_N)

Ach reversal experiment using anesthetized cat blood pressure



- Small dose of Ach → ↑ blood pressure due to → "vasodilatation and bradycardia"
 - Higher dose of Ach → **Further** ↑ in blood pressure
 - **Atropine** → **block** muscarinic receptors, so:
 - **Small dose** of Ach after **atropine** → gives no effect
 - **At high dose** of Ach after **atropine** → ↑ blood pressure **due to**:
1. Stimulation of N_N receptor in adrenal medulla release of NA and AD → "Vasoconstriction and tachycardia" → ↑ blood pressure
 2. Stimulation of N_N receptor in sympathetic ganglia
- # Muscarinic actions of Ach are stronger, so they mask nicotinic actions
Stimulation of nicotinic receptor needs high doses of Ach

Use of Ach

Not used now due to

- 1- Not effective orally (Must be parenteral)
- 2- Short duration of action
- 3- Non selective (Muscarinic & Nicotinic actions)

So, used as experimental tool

1- Parasympathomimetics

Called also → Cholinergic drugs / Cholinomimetic drugs

Are drugs which stimulate muscarinic receptors (PCR)

Directly acting

1) Choline esters

Acetylcholine
Carbachol
Methacholine
Bethanecol

2) Cholinomimetic alkaloids

Pilocarpine
Muscarine
Arecoline

3) Anticholinesterases

Indirectly stimulate muscarinic receptors

Reversible

Physostigmine
Neostigmine
Neostigmine substitute

Irreversible

Organophosphorous compounds

B- Effect of Ach on Skeletal muscles

Stimulation of N_M receptor in motor end plate of skeletal muscles → causes **muscle twitches**

DEP : Di-isopropyl fluorophosphate

TEPP : Tetraethyl pyrophosphate

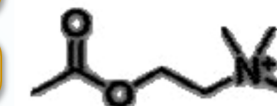
Nerve gases : Tabun - Suman - Sarin

Insecticides :
Parathion - Malathion - Fenthion

1- Parasympathomimetics

1) Choline esters

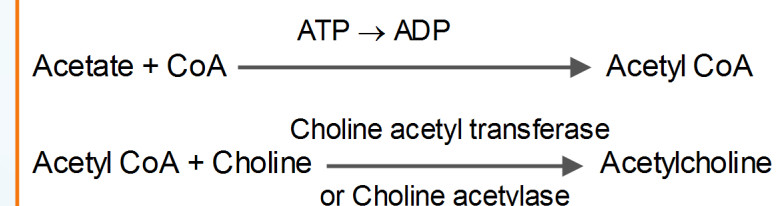
I. Acetylcholine



Acetylcholine (Ach) is a neurotransmitter at

- 1- Neuromuscular junction (N_M)
- 2- Autonomic ganglia (N_N)
- 3- Preganglionic nerve to adrenal medulla (N_N)
- 4- Postganglionic parasympathetic nerve endings (M)
- 5- Postganglionic **sympathetic** nerve endings of **sweat glands** (M)
- 6- Some areas in CNS (M)

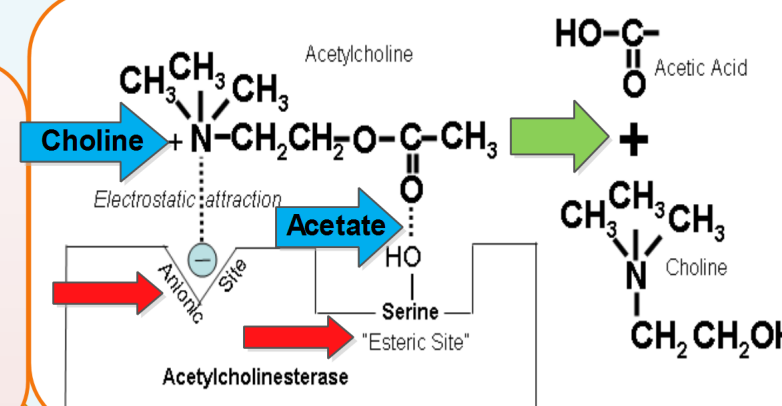
Synthesis of Ach in nerve terminal



Hydrolysis of Ach by cholinesterases

True cholinesterase (acetylcholinesterase)	Pseudocholinesterase (Butyrylcholinesterase)
<u>Specific</u> : Hydrolysis of Ach and methacholine	<u>Non-specific</u> : Hydrolysis of Ach, Succinylcholine and procaine
<u>Site</u> : Cholinergic sites and CNS	<u>Site</u> : Blood and liver

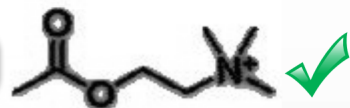
Acetylcholine has a **short duration of action** as it is rapidly hydrolysed by cholinesterase into **Acetate + Choline**



1- Parasympathomimetics

1) Choline esters

I. Acetylcholine



Resist hydrolysis by cholinesterase → more stable

Properties

- Longer duration of action
- Active orally and parenterally
- More selective

II. Synthetic choline esters

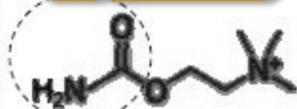
Types of modification

β -methylation of Ach → ↑ selectivity to muscarinic activity ex. Methacholine

Carbamate ester → resist hydrolysis by cholinesterase → longer duration of action ex. Carbachol

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1- Carbachol



Structure

Modifications

Carbamate instead of ester

Properties

1. Resist hydrolysis by cholinesterase enzyme → so it has longer duration of action
2. Non selective → has muscarinic and nicotinic actions
3. Due to non selectivity → it is used locally in the eye → miosis and ↓ IOP

Uses

Used in **glucoma** (increased intraocular pressure)

2- Methacholine

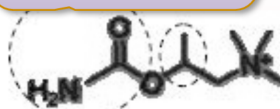


β -methylation

Selective muscarinic actions "NO nicotinic actions", it is more selective to CVS → decrease heart rate & Vasodilatation

1. Paroxysmal atrial tachycardia
2. Raynaud's disease (peripheral vasoconstriction)

3- Bethanecol



Both modifications

1. Selective muscarinic actions "NO nicotinic actions", it is more selective to smooth muscles (GIT - Urinary bladder - Eye)
2. Resist hydrolysis by cholinesterase enzyme → so it has longer duration of action
3. Active orally

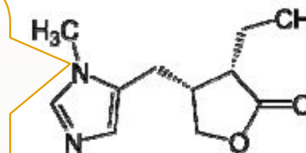
1. Retention of urine → postoperative & postpartum
2. GIT disorders → paralytic ileus → gastric atony
3. Ophthalmic → Glucoma

2) Cholinomimetic alkaloids

Pilocarpine

Properties

1. Tertiary amine → lipid soluble → that means it can cross BBB → causes CNS stimulation (so, used locally in the eye)
2. It has mainly muscarinic effects
3. NOT hydrolyzed by cholinesterase enzyme → long duration of action



Mechanism of action

Direct stimulation of muscarinic receptors

Pharmacological actions

1. CNS → Cortical stimulation → irritability - nervousness - insomnia → so, used locally on the eye
2. GIT → ↑ tone and motility (Peristalsis)
3. Urinary bladder → evacuation
4. Bronchi → bronchoconstriction
5. ↑ Secretion of exocrine glands →
 - a) ↑ Saliva (sialagogue)
 - b) ↑ Sweat (diaphoretic)
6. Eye →
 - a) Contraction of circular muscles of iris (constrictor pupillae muscles) → miosis → widening of angle of filtration (angle of anterior chamber) → drainage of aqueous humour → ↓ IOP
 - b) Contraction of ciliary muscles
 - 1- accommodation for near vision
 - 2- opening of canal of schlemm → ↑ drainage of aqueous humour → ↓ IOP

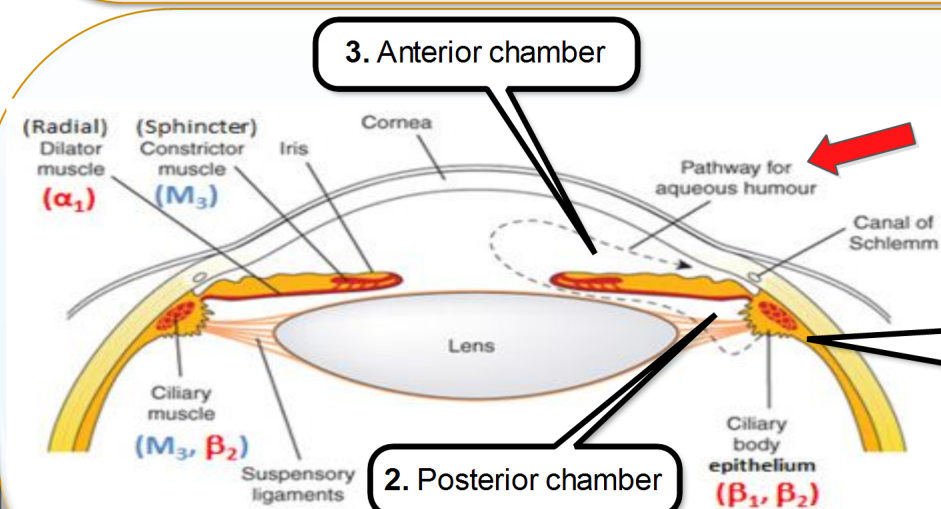
Therapeutic uses

1. Glaucoma
2. Overcome mydriatic action produced by atropine
3. Antidote to atropine overdose
4. Alternative with mydriatics → to break adhesion between iris and lens
5. Stimulate salivation in patients with dry mouth
6. Promote hair growth (not autonomic function) !

Intraocular pressure

It increases when the rate of aqueous humor secretion becomes more than its drainage (equilibrium imbalance) → leading to **glucoma** (IOP ↑) → this can cause extra pressure on optic nerve → may lead to irreversible blindness

Secretion > Drainage



Glaucoma

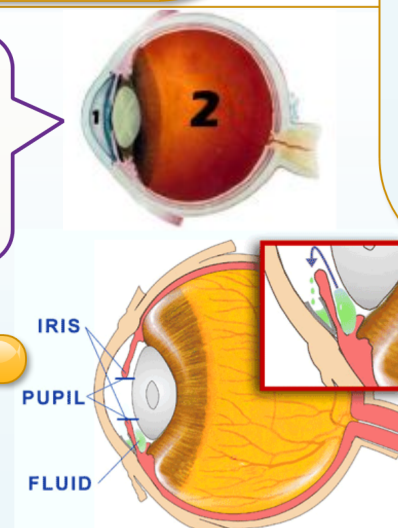
4. Drainage at angle of filtration and canal of schlemm

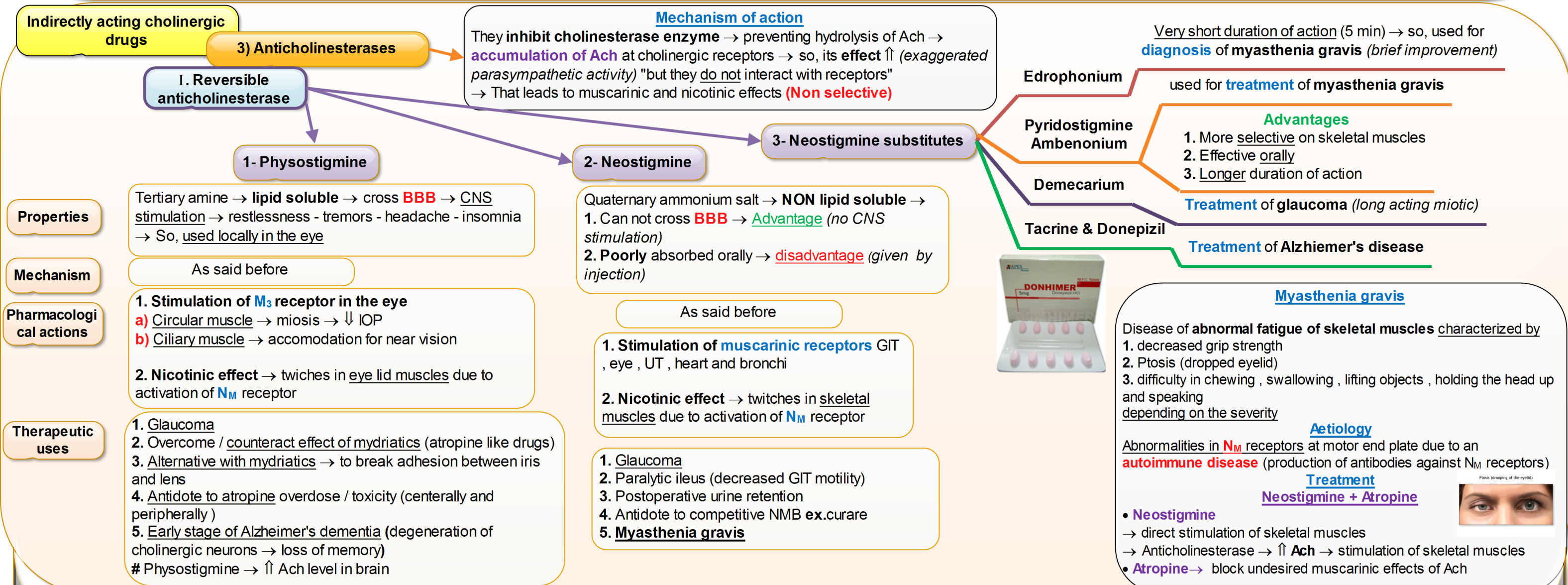
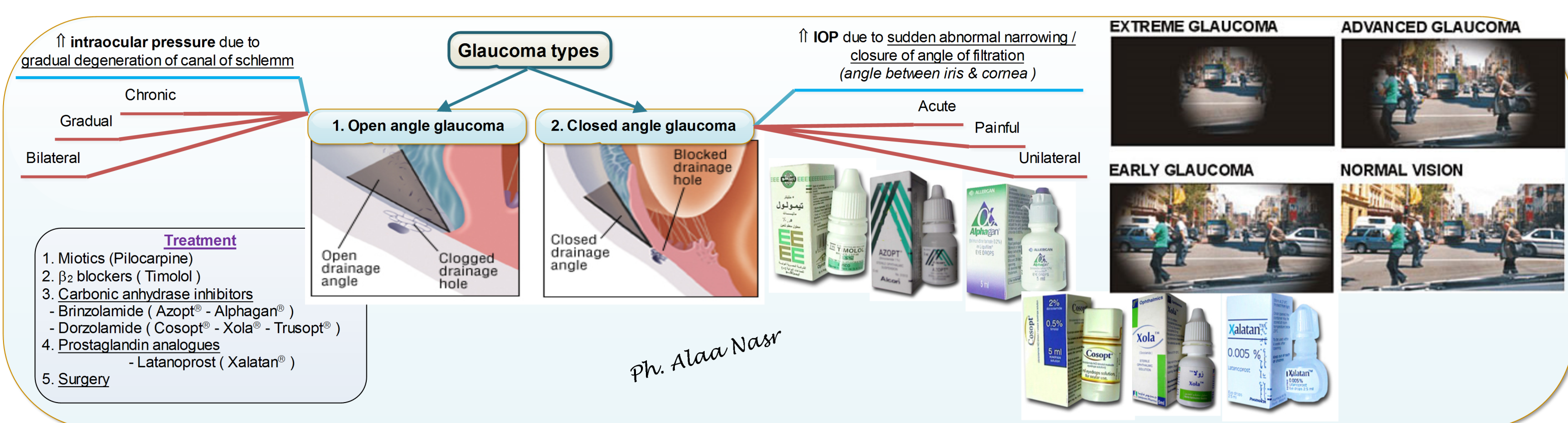
1. Aqueous humour Secreted from ciliary body

Types of humors in the eye

- 1- Aqueous humor (between cornea and lens)
- 2- Vitrous humor (in the eye mass)

Normal





3) Anticholinesterases

II. Irreversible anticholinesterase

Organophosphates

Mechanism

- They form **strong covalent bond** with **cholinesterase** enzyme → leading to **permanent inactivation** of the enzyme
- Enzymatic activity is returned by **synthesis of new enzyme** !

Therapeutic uses

1. **DFP (diisopropyl fluorophosphate)** → used in treatment of **glaucoma**
2. **Insecticides** → Parathion - Malathion - Fenthion
3. **Nerve gases** → Tabun - Soman - Sarin (**war gases**)

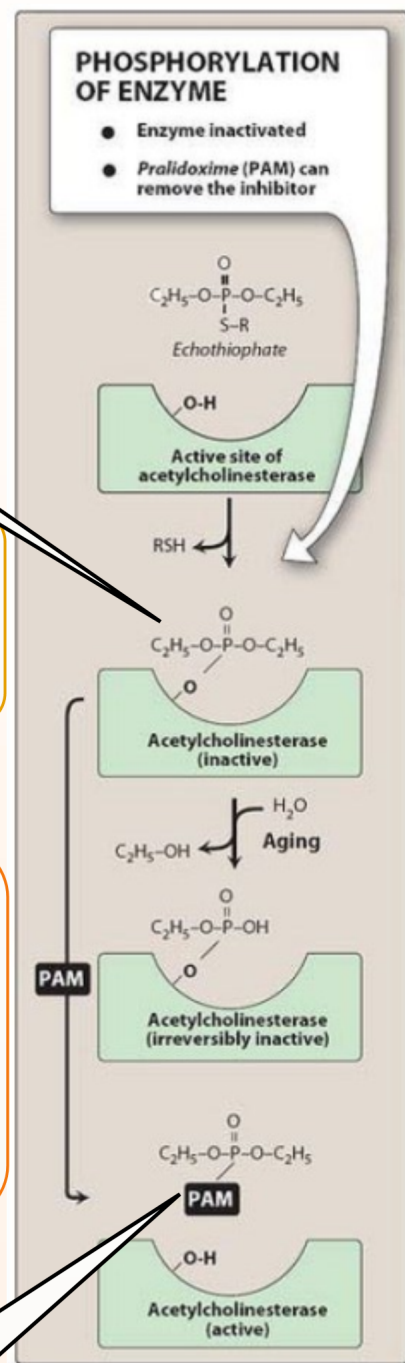
Toxicity

1. **SLUD syndrome** → Salivation + Lacrimation + Urination + Diarrhea
2. Severe bronchospasm
3. Bradycardia
4. Miosis
5. Skeletal muscle twitches
6. **CNS stimulation** → tremors - convulsions - confusion
→ depression of cardiovascular and respiratory centers

Treatment of toxicity

1. Atropine
2. Cholinesterase re-activator as **Pralidoxime (PAM) - Diacetylmonoxime (DAM)**
→ Combine with phosphate of organophosphorous compounds → *leave cholinesterase free*
→ Must be given **within 3-4 hours (before aging of the enzyme)** → organophosphate **binds** to cholinesterase enzyme and **loses one of its alkyl group**

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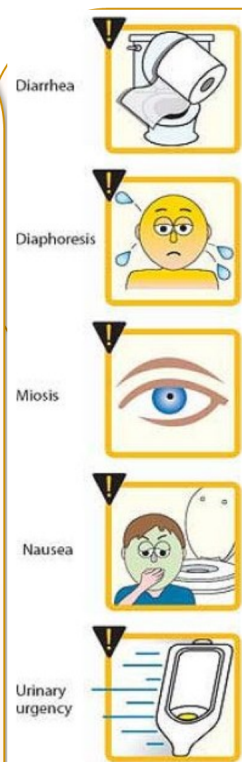


Side effects of cholinergic drugs

1. Sweating (diaphoresis)
2. Salivation
3. Hypotension
4. Nausea, diarrhea and abdominal pain
5. Urinary urgency
6. Bronchospasm

Contraindications of parasympathomimetics

1. **Peptic ulcer** → as they increase gastric acid secretion
2. **Bronchial asthma** → as they may induce **bronchospasm**
3. **Coronary insufficiency** → as they may cause **hypotension** → leading to further decrease in coronary blood flow



Parasympathetic antagonist Anticholinergic drugs Antimuscarinic drugs

Are drugs which block *muscarinic action of Ach* and related drugs by blocking **muscarinic receptors (PCR)**

2- Parasympatholytics

II. Hyoscine (Scopolamine)

Similar to atropine in action

Shorter duration of action

Effect is more pronounced on the eye and exocrine glands

Sedation and hypnosis

Amnesia (temporarily loss of memory)

Anti motion sickness

- So used as preanesthetic medication
- Decrease the dose of general anesthetic

Differs from atropine in

Mainly CNS depressant

Mechanism

Reversible competitive antagonist of Ach at muscarinic receptors
Antagonism effect is overcome by increasing Ach level ex. using anticholinesterases

Pharmacological actions

Antiemetic (inhibit vomiting center)

Antiparkinsonian (decrease tumors)

Therapeutic doses

Toxic doses

CNS stimulation

Due to block of M₃ receptor in **circular muscle** → **Passive mydriasis**

Mydriasis

So contraindicated in glaucoma patients

Increase IOP

Due to block of M₃ receptor in **ciliary muscle** (causing paralysis in it) → **loss of accommodation for near vision**

Cycloplegia

Loss of light reflex

Normal reflex to light is lost due to the **paralysis of circular muscles** (responsible for miosis)

↓ **secretions** → salivary (Xerostomia → dry mouth),
↓ bronchial secretion and lacrimation

↓ **Sweat body** → ↑ temperature → **atropine fever**

Exocrine glands

M₂ Heart rate ↑ Tachycardia +ve chronotropic effect

No effect on blood pressure **No parasympathetic innervation**

↓ HCl release
↓ Tone & motility

Constipation

Relaxation of detrusor muscle

Urine retention

Contraction of sphincter muscle

Relaxation of ureter muscle (antispasmodic)

Bronchodilatation & ↓ Secretion

2- Parasympatholytics

III. Synthetic atropine substitutes

Mydriatics

1. Homatropine
2. Eucatropine
3. Tropicamide (Mydrapid®)
4. Cyclopentolate (Plegica®)

They do not have to be selective as they are administered locally in the eye



Antisecretory / Antispasmodic

1. Hyoscin butyl bromide (Buscopan®)
2. Propantheline
3. Oxyphenonium
4. Atropine methylnitrate

They are used for colics (intestinal - renal - biliary)



Antiparkinsonian

1. Benztropine (Cogintol®)
2. Benzhexol

Must be lipophilic to cross BBB



For bronchial asthma / bronchodilator

1. Ipratropium (Atrovent® - Combivent®)
2. Oxitropium



Urinary bladder relaxants

1. Oxybutenin (Uripan®)
2. Tolterodine (Uricontrol®)

They are selective M_3 receptors blockers (in detrusor muscle of urinary bladder)
Used in treatment of urine incontinence and nocturnal enuresis



Therapeutic uses of antimuscarinic drugs

GIT

1. Antispasmodic:
Colics (intestinal - biliary) - diarrhea - irritable colon
 2. Antisecretory: in peptic ulcer
- # Pirenzepine (selective M_1 blocker) is preferred over atropine in peptic ulcer

CNS

- a) Preanesthetic medication:
Hyoscine is more preferred due to:
 1. amnesia
 2. antisecretory
 3. protect heart from vagal effect
- b) Antiparkinsonian:
↓ tremors and rigidity

Ophthalmology

1. Fundus examination:
Mydriasis → to examine retina and optic disc
2. Alternative with miotics: to break adhesion between iris and lens

Urinary tract

1. Urinary incontinence
2. Nocturnal enuresis
3. Antispasmodic for renal colics

Prophylaxis against motion sickness

Hyoscine is the drug of choice

Respiratory

- Bronchodilators in bronchial asthma
- Disadvantage** → atropine produce **viscid thick sputum** → difficult to expel

Antidote for poisoning by

Mushrooms - Neostigmine - Physostigmine - Organophosphates

CVS

- Carotid sinus bradycardia
hyperactive carotid sinus → reflex bradycardia

Skin

For treatment of hyperhidrosis (excessive sweating)

Adverse effects and toxicity of atropine

1. Tachycardia (rapid pulse)
2. Mydriasis (Dilated pupils) → photophobia
3. Dry mouth
4. Flushed skin
5. High body temperature (atropine fever) specially in children
6. CNS (restlessness - confusion)
7. Urine retention

Antidote: Physostigmine (can cross BBB) or Pilocarpine

Contraindications of antimuscarinics

1. Glaucoma
2. Enlarged prostate (prostatic hypertrophy) may cause urine retention
3. Angina pectoris as atropine causes tachycardia
4. Paralytic ileus
5. Esophageal reflux

Ph. Alaa Nasr

3- Sympathomimetic

Are drugs which stimulate adrenergic receptors (PCR) → produce effects similar to sympathetic nerve stimulation

Classification

1. Catecholamines

- 1) Adrenaline
- 2) Noradrenaline
- 3) Dopamine
- 4) isoprenaline

A- Chemically

2. Non catecholamines

- 1) Ephedrine
- 2) Amphetamine
- 3) Phenylephrine
- 4) Tyramine

B- According to mechanism of action

1. Direct

Drugs stimulate α or β receptors directly

ex. 1. Adrenaline , 2. Noradrenaline
3. isoprenaline , 4. Phenylephrine

2. Indirect

Drugs act by release NA from nerve terminal then NA stimulate adrenergic receptors

ex. 1. Amphetamine , 2. Tyramine

3. Dual / Mixed action

Drugs act by both direct and indirect mechanisms

ex. Ephedrine

I. Catecholamines

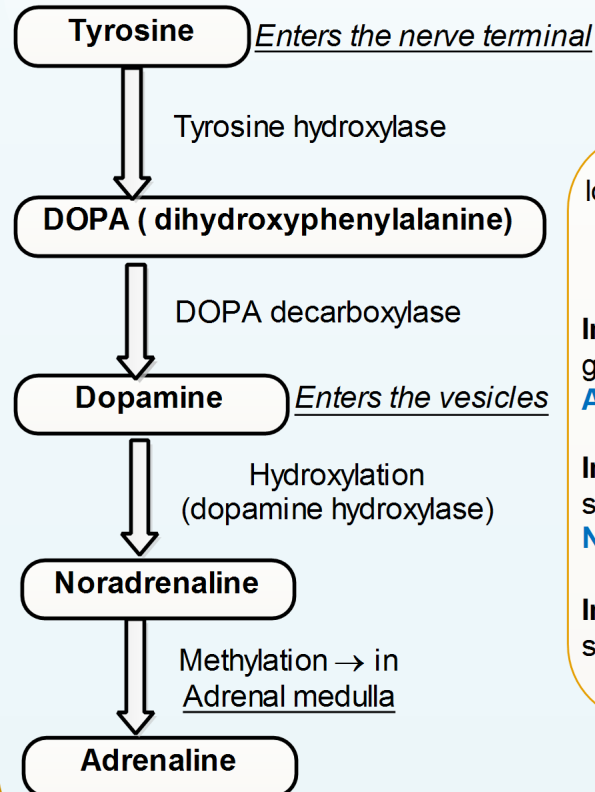
- They are called catecholamines as they contain catechol (3,4-dihydroxyphenyl group) in their structures.
- They are derived from the amino acid "Tyrosin"

1- Adrenaline (Epinephrine)

- Directly acting
- Stimulate all adrenergic receptor α and β receptors
- Secreted from the **adrenal medulla**

Adrenal medulla secretes 80% Adrenaline and 20% Noradrenaline

1) Synthesis



These steps occur in different locations in the body but it stops at a suitable product to produce a suitable function !

In adrenal medulla → the synthesis goes to the end (formation of **Adrenaline / Epinephrine**)

In symaphetic nerve endings → it stops at the formation of **Noradrenaline**

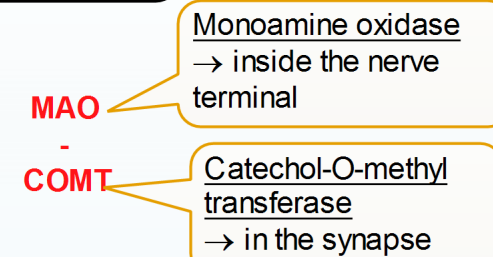
In dopaminergic neurons → it stops at the formation of **dopamine**

ph. Alaa Nasr

2) Termination of action

a. Enzymatic destruction

Adrenaline , Noradrenaline & all catecholamines



3-methoxy, 4-hydroxy mandelic acid
Vanillyl mandelic acid (VMA)

VMA can be used as a pheochromocytoma marker !!

Pheochromocytoma → is a tumor of adrenal medulla → causes secretion of LARGE amount of adrenaline → that leads to hypertension

So HOW can it be used as a marker !

VMA is excreted in urine in a normal level → 2-6 mg/ 24 hrs
in case of pheochromocytoma → the level increases can exceed 50 mg/ 24 hrs !

b. Uptake mechanisms

Most of released NA undergoes neuronal uptake after performing their actions

1. Neuronal uptake (Uptake 1)

Blockers → Cocaine , Guanethidine increase NA level at receptors' site

2. Extraneuronal uptake (Uptake 2)

Catecholamines go to tissues

Blockers → Phenoxybenzamine

3. Granular uptake (Uptake 3)

Catecholamine is taken up from the cytoplasm (inside the nerve terminal) → to be stored in vesicles

Blockers → Reserpine

3) Absorption of adrenaline

Oral

Poor absorption → rapid destruction by intestinal enzymes

Parenteral

Slow absorption → due to local vasoconstriction (α_1 stimulation → ↓ blood flow → ↓ absorption)

Subcutaneous SC

Rapid absorption → due to vasodilatation of skeletal muscles blood vessels (β_2 stimulation → ↑ blood flow → ↑ absorption)

Intramuscular IM

Used for its **local effect** on respiratory tract

inhalation

1- Adrenaline (Epinephrine)

Synthesis

Termination of action

Absorption of adrenaline

Pharmacological actions

A. Local actions

1. Mucous membranes

Vasoconstriction (α_1 stimulation) so used as

- Hemostatic** → produces vasoconstriction which ↓ bleeding → so can be applied to bleeding surfaces
- Decongestant** → applied locally in the nose → ↓ congestion by vasoconstriction in nasal blood vessels
- Used with local anesthetics** → produces vasoconstriction → ↓ absorption → prolongs the effect of anesthetics

2. Eye

limited effect as adrenaline is destroyed by alkaline tears
Adrenaline ↓ formation of aqueous humor and ↓ IOP

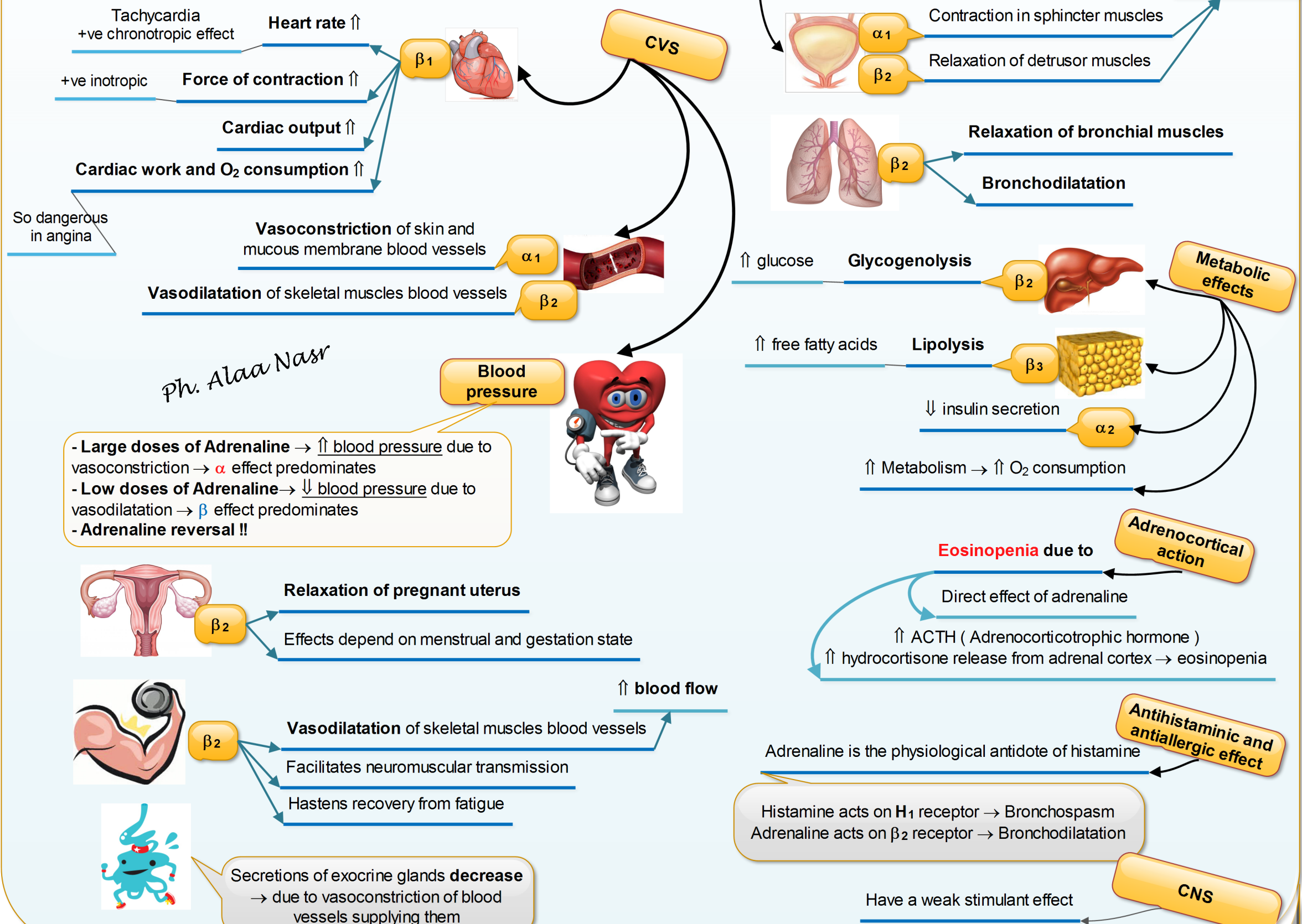
B. Systemic actions

Adrenaline directly stimulate both α and β receptors

The effect produced depends on

1. Concentration of adrenaline
2. Type of receptor

- ♦ At **high** concentration → α effect predominates
- ♦ At **low** concentration → β effect predominates



1- Adrenaline (Epinephrine) (AD)

Synthesis

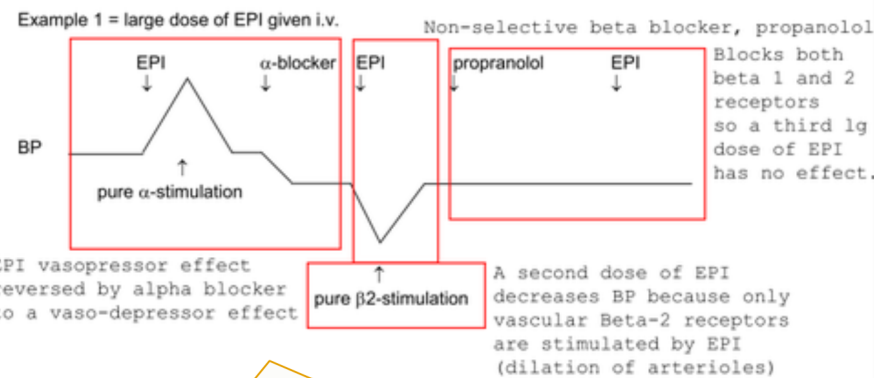
Termination of action

Absorption of adrenaline

Pharmacological actions

Adrenaline reversal !

Using anesthetized cat blood pressure



Normally

NA acts on: $\alpha - \beta_1$ → causing hypertension

AD acts on: $\alpha - \beta_1 - \beta_2$ → causing hypertension

After using α blocker

NA → effect is abolished

AD → "no α effect" - β_1 - β_2 → Vasodilatation → hypotension "

So, in the presence of α blocker AD causes hypotension as it acts only on β_2 receptors

Therapeutic uses of adrenaline

1. **Bronchodilators** in bronchial asthma and bronchitis
2. **Nasal decongestant**
3. AD is **used with local anesthetics** to delay absorption, so prolong duration of action
4. **Allergy and hypersensitivity** → AD is used in case of anaphylactic shock (AD is a physiological antidote of histamine)
5. **Insulin hypoglycemia**
6. **Local hemostatic** → used topically to decrease oozing of capillary blood vessels (ex. nasal bleeding)
7. **Cardiac resuscitation** (AD may be injected intracardiac)
8. **Glaucoma**

Contraindications

1. **Hypertension** AD may lead to cerebral hemorrhage
2. **Coronary diseases** (coronary arteries give the heart low amount of blood) → so it can not withstand the excess work produced by AD "↑ O_2 demand" → leading to anginal attacks
3. **Hyperthyroidism** → due to high production of adrenergic receptors on blood vessels
4. **General anesthesia** → as anesthetics potentiate the effect of AD on the heart leading to cardiac arrhythmia
5. **Patients receiving digitalis** (digitalized patients) as their hearts exert more work so AD would make their hearts exert more and more work !

2- Noradrenaline (Norepinephrine) (NA)

Released from

1. NA is the neurotransmitter released at postganglionic sympathetic nerves
2. NA represents 20% of adrenal medulla secretions

Routes of administration

ONLY by IV infusion

NOT given SC injection → as NA has a strong vasoconstriction effect that may lead to necrosis of skin and SC tissues

NOT given by IV injection may → cause cardiac arrest

Mechanism of action

NA stimulates

α receptors → **MAINLY**

β_1 receptors → to lesser extent and has **NO EFFECT** on β_2 receptors

Effect of NA on CVS

1. **Blood vessels** → generalized vasoconstriction → α_1 effect and no β_2 effect
2. **Blood pressure** → increases systolic and diastolic
3. **Heart** → a) increase force of contraction (+ve inotropic effect)
b) **Reflex bradycardia !** (to compensate the vasoconstriction increasing blood pressure)

Therapeutic uses

Pressor agent

Used in controlling hypotension during spinal anesthesia

Simplified

Noradrenaline

Adrenaline

Isoprenaline

$\alpha \beta$

$\alpha \beta$

$\alpha \beta$

3- isoprenaline

Synthetic drug → isopropyl noradrenaline
Mainly metabolized by COMT and poorly by MAO

Mechanism of action

Non-selective β agonist directly → stimulates β_1 and β_2 receptors and has **NO EFFECT** on α receptors

Pharmacological actions

CVS β_1

1. increase heart rate (+ve chronotropic)
2. increase force of contraction (+ve inotropic)
3. increase cardiac output
4. **Blood pressure** → slight or no change (no vasoconstriction)

Smooth muscles β_2

1. Bronchodilatation
2. Decrease tone and motility of intestine and urinary bladder
3. Relaxation of human pregnant uterus

Therapeutic uses

1. Cardiac stimulant (in case of bradycardia)
2. Bronchodilator (rarely used in asthma **"NON-SELECTIVE"** → causes tachycardia and palpitations)

4. Dopamine

- Dopamine is precursor for NA (as illustrated before)
- Dopamine is synthesized and released from dopaminergic nerves
- It is also an important neurotransmitter in CNS

Types of dopamine receptors

- D_1 → Peripheral receptors → its stimulation causes vasodilatation
- D_2 → central receptors → responsible for the neurotransmitter function in CNS

Pharmacological actions

Dopamine can work also on α_1 and β_1 receptors
($D_1 > \beta_1 > \alpha_1$)

so, its action will differ according to the used concentration

Low dose

Stimulation of D_1 receptors in renal and mesenteric blood vessels
→ vasodilatation → increase blood flow to kidneys and viscera

Moderate doses

Also stimulation of β_1 receptors in the heart → +ve inotropic effect (↑ force of contraction)

High doses

Also stimulation of α_1 receptors → Vasoconstriction and indirect effect → NA release from nerve terminals

Therapeutic uses

1. **Cardiogenic shock (shock causes heart to stop)**
As dopamine stimulate β_1 receptors → +ve inotropic and D_1 receptors → increase renal blood flow → so avoid renal shut down
2. **Chronic refractory congestive heart failure**
3. **Hypovolaemic shock**
4. **Can be used in kidney failure** (renal vasodilatation)

5. Dobutamine

- Dopamine analogue
- Dobutamine **does not act on dopaminergic receptors** !!
- Dobutamine is a **selective β_1 agonist**
its inotropic effect is > Chronotropic effect

Therapeutic uses

Used in congestive heart failure → improve myocardial function with minimal change in heart rate → which is an advantage of dobutamine over other sympathomimetics → **less O_2 demand**

AD, NA, Dopamine → **Natural**
isoprenaline, Dobutamine → **Synthetic**

II. Non catecholamines

1. Ephedrine

1. Natural alkaloid obtained from Ephedra plants and can be prepared synthetically
2. Resistant to MAO and COMT (as it is non catecholamine) so, it has **long duration of action**
3. **Effective orally**
4. It is a tertiary alkaloid Lipid soluble so, it can cross BBB so, it has **CNS stimulant effect**

Mechanism of action

Dual (mixed) action

1. Direct

Stimulation of adrenergic receptors → both α and β receptors

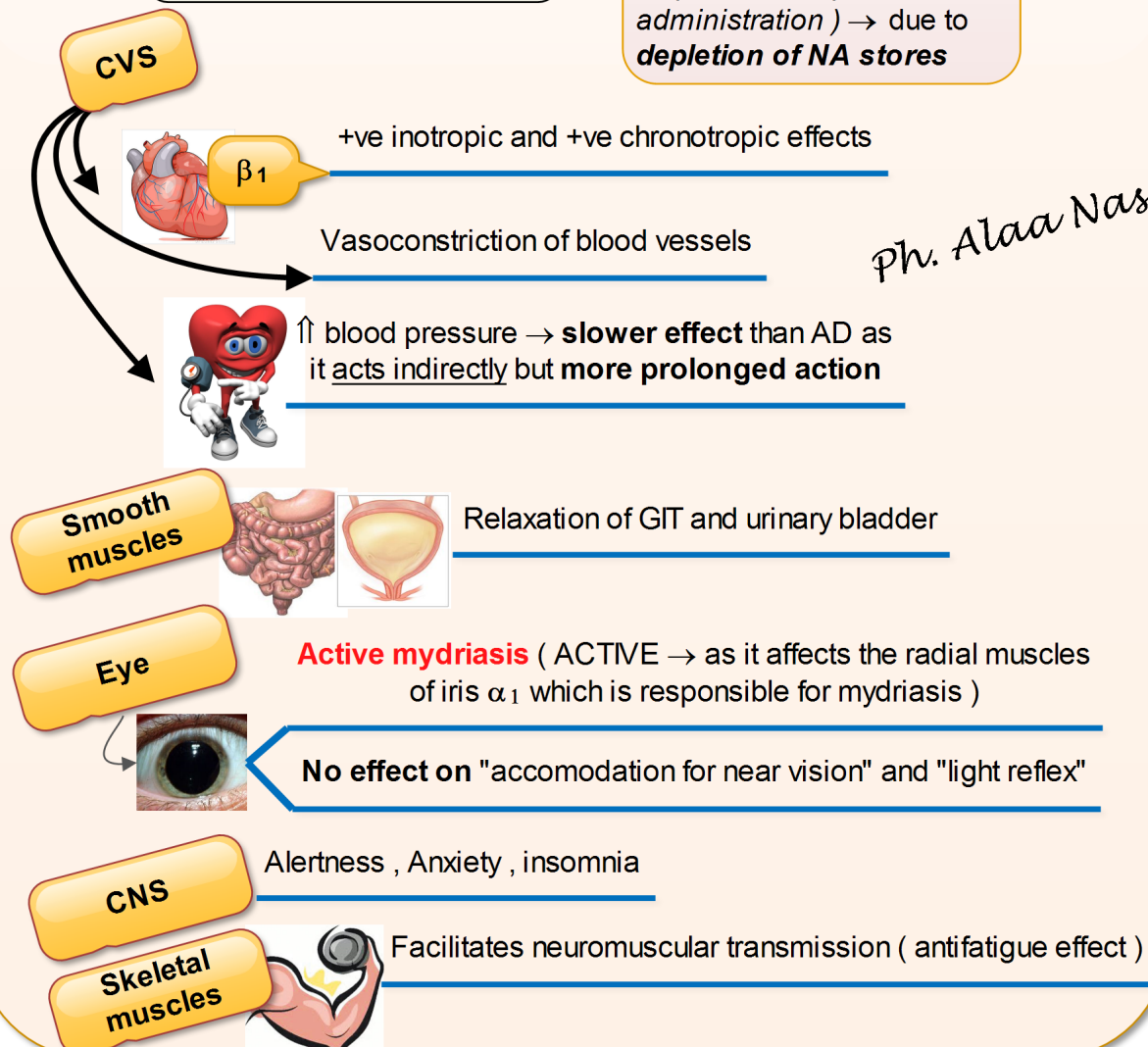
2. Indirect (main action)

increase NA release from sympathetic nerve terminals → then NA act on both α and β_1 receptors

Pharmacological actions

Similar to adrenaline !

Repeated administration of Ephedrine produces tachyphylaxis (decreased response on repeated administration) → due to **depletion of NA stores**



Therapeutic uses

1. **Prophylactic** in bronchial asthma
Not used in acute attacks of asthma → as it has delayed onset of action (because of its indirect effect)
2. **Nasal decongestant**
3. **Pressor agent in spinal anesthesia** (to reverse hypotension)
4. **Mydriatic**
5. **Narcolepsy** مرض النوم المفاجئ
6. **Anorexigenic** (appetite suppressant)

Side effects

1. insomnia (abused for this action → more studying at night !)
2. Urine retention in elderly patients with enlarged prostate
3. Tachyphylaxis

2. Amphetamine

- Synthetic indirectly acting sympathomimetic
- Rapidly absorbed from GIT
- Not hydrolysed by MAO or COMT
- Can cross BBB so, it is a **potent CNS stimulant**
- **produces tolerance**

Mechanism of action

Indirectly acting

increase NA release from sympathetic nerve terminals

Pharmacological actions

1. **Psychic stimulation** (euphoria - increases mental and physical activities)
2. **Analeptic** (increase alertness)
3. **Antifatigue action** (abused by athletes to give extra power !)
4. **Anorexigenic** (appetite suppressant)
5. **Mild analgesic action**
6. **Tolerance and development of addiction**

Therapeutic uses

1. **Attention deficit hyperactivity disorder ADHD in children**
→ Here the child suffers from lack of giving attention at any activity, hyperkinetic (hyper mobility / hyperactive), nervousness .. etc
→ Amphetamine can manage this case paradoxically (illogically) (paradoxical effect)
2. **Narcolepsy** مرض النوم المفاجئ

Selective adrenergic agonists

Selective α_1 agonists

Phenylephrine
Methoxamine

Direct stimulants to α_1 receptors

→ so produces vasoconstriction and mydriasis

Therapeutic uses

1. Nasal decongestant (Afrin®)
2. Mydriatics
3. Pressor agents in spinal anesthesia
4. Local vasoconstrictor with local anesthetics (to reduce systemic absorption and prolong the action)



Selective α_2 agonists

Clonidine (Catapress®) (rarely used now due to its side effects)
Methyldopa (Aldomet®)

Stimulants presynaptic α_2 receptors

→ Decreases NA release

Therapeutic uses

Treatment of hypertension



Selective β_2 agonists

Salbutamol (Ventolin®)
Terbutaline

It can be used orally or by inhalation (to give a
→ stimulates β_2 receptors in bronchi → produces bronchodilatation

Therapeutic uses

Treatment of acute attacks of bronchial asthma

Formoterol & Salmeterol → Long-acting β_2 -agonist
→ used in management of asthma but not in acute attacks



Ritodrine (Yutobar®)

Selective β_2 agonist → used as a myometrial relaxant (relax the uterus) during pregnancy
So, can be used in premature labour



4- Sympatholytics

I. α adrenergic blockers

a) Non selective α blockers

1. Ergot alkaloids

a- Ergotoxine

- α blocker → vasodilatation → decrease blood pressure

Therapeutic uses

1. Hypertension
2. Cerebral ischemia (to increase cerebral blood flow)
3. Raynaud's disease (peripheral vascular disease)

Dihydroergotoxin is a potent α blocker

Other ergot alkaloids have no α blocking effect but let's talk short notes about them

b- Ergotamine

- Potent and direct vasoconstrictor but weak α blocker

Therapeutic uses

Used to treat migraine attacks (by inducing vasoconstriction of cranial blood vessels → reverse the cranial vasodilatation of migraine headache)

Cafergot → ergotamine + Caffeine → Synergistic effect
→ used for treatment of migraine

c- Ergometrine

- Oxytocic → potent stimulation of uterine muscles
→ increase contraction of uterus

Therapeutic uses

- Used in obstetrics
1. induction of labour
 2. prevent postpartum haemorrhage

Methylergometrine is a powerful oxytocic

2. Phenoxybenzamine

Potent non selective α blocker (block both α_1 and α_2)

Mechanism of action

1. irreversible competitive antagonist (covalent binding) at α receptors
2. Slow onset and long duration of action (3 - 4 days)
3. Antihistaminic , antiserotonin (5HT) and anticholinergic actions

Therapeutic uses

1. Raynaud's disease (vasoconstriction in peripheral vascular diseases)
2. Pheochromocytoma

Side effects

1. Postural / orthostatic hypotension
2. Reflex tachycardia
3. Failure of ejaculation

3. Phentolamine & Tolazoline

Potent non selective α blocker (block both α_1 and α_2)

Mechanism of action

Reversible competitive antagonist at α receptors

Therapeutic uses

1. Raynaud's disease
2. Pheochromocytoma
3. Frostbite

Tachycardia produced by non selective α blockers (Phentolamine and Phenoxybenzamine) happens due to

1. Reflex tachycardia → baroreceptors (receptors sensitive to blood pressure) → when it detect hypotension → it induces reflex tachycardia ($\uparrow$ heart rate) to increase blood pressure again
2. Blocking α_2 receptors → increase NA release → sympathetic stimulation of the heart → tachycardia

b) Selective α blockers

1. Selective α_1 blockers

- Prazosin
- Terazosin
- Doxazosin

They block α_1 receptors with no effect on α_2 receptors

→ They cause vasodilatation so decrease blood pressure

They cause very little tachycardia as they have no effect on α_2 receptors

Therapeutic uses

1. Hypertension
2. Benign prostatic hyperplasia (act by blocking α_1 receptors in bladder neck sphincter → relaxation of sphincter muscle → improve urine outflow

Other selective α_1 blockers

1. Tamsulosin

Highly selective to block α_{1A} receptors rather than α_{1B} receptors
→ so, used mainly in treatment of benign prostatic hyperplasia (BPH)

Types of α_1 receptors

- a. α_{1A} receptors → found in the sphincter of urinary bladder
- b. α_{1B} receptors → in blood vessels

2. indoramin

α_1 blocker with direct myocardial suppressant action → so, no reflex tachycardia

2. Selective α_2 blockers

Yohimbine

→ increase NA release from sympathetic nerve terminals

Therapeutic uses

1. Aphrodisiac (treatment of male sexual dysfunction and impotence) (not used now)
2. Experimental tool



4- Sympatholytics

I. α adrenergic blockers

II. β adrenergic blockers

1. Non selective β blocker block both β_1 and β_2

With ISA

Pindolol
Oxyphenolol

no ISA

Propranolol
Nadolol

2. Cardioselective selective β_1 blocker

With ISA

Acebutalol

no ISA

Atenolol

3. Selective β_2 blocker

Butoxamine
used as an experimental tool

ISA (intrinsic sympathomimetic activity) → partial agonist so, they will not produce severe bradycardia

Non-selective β blockers can not be used in asthmatic patients as they block β_2 receptors which are responsible for bronchodilatation!

Cardioselective β_1 blockers and also β blockers with ISA can be used in asthmatic patients

Drugs blocking both α and β receptors

Labetalol

1. Decrease cardiac output (CO) → β blocking effect
 2. Decrease peripheral vascular resistance due to → α blocking effect (vasodilatation)
- # it has rapid onset of action and used in treatment of hypertension

Propranolol

1. Pharmacokinetics

- Completely absorbed from GIT
- Metabolized in liver
- Excreted in urine
- Half-life $t_{1/2}$ = 3 - 10 hrs for most β blockers

2. Mechanism

- Non selective β blockers without ISA
- Has membrane stabilizing action (local anesthetic - quinidine like action)

3. Pharmacological actions

CVS

1. Bradycardia
2. ↓ force of contraction
3. ↓ Cardiac output (C.O)
4. Antiarrhythmic action (quinidine like action)
5. ↓ Blood pressure due to
 - a) ↓ C.O
 - b) ↓ Renin release → ↓ angiotensin → ↓ vasoconstriction (renin is released from juxtaglomerular cells through β_1 stimulation)

Bronchi

Bronchoconstriction / Bronchospasm due to blocking of β_2 receptors in bronchi

Metabolic

Blocking β_2 receptors in liver inhibit glycogenolysis

4. Therapeutic uses

1. Cardiac arrhythmia (↓ heart rate)
2. Prophylactic (prevention) against anginal attacks → ↓ cardiac work so ↓ O_2 demand
3. ↓ Prophylaxis against myocardial infarction (prevent arrhythmia in patients with MI)
4. Hypertension (delayed response)
5. Glaucoma (by blocking β_2 receptors in ciliary body leading to ↓ secretion of aqueous humor so ↓ IOP (Timolol is preferred in treatment of glaucoma))
6. Prophylactic against migraine
7. Hyperthyroidism / Thyrotoxicosis / Thyroid storm → used preoperatively to protect against tachycardia
8. Pheochromocytoma .. combined with α blocker before surgery
9. Anxiety states as palpitation and tremors associated with sympathetic overactivity such as stage fright

5. Side effects

1. Severe bradycardia and hypotension
2. Heart failure in case of inadequate myocardial function
3. Bronchospasm
4. Augments (strengthen) hypoglycemic effect of insulin (↓ glycogenolysis) in diabetic patients + β blocking masks hypoglycemic alarms (tachycardia - tremors - anxiety)
5. Fatigue - dizziness - muscle aches
6. Night mares
7. Allergic reactions
8. Cold hands

6. Contraindications

1. Congestive heart failure
2. Bronchial asthma
3. Partial heart block

4- Sympatholytics

I. α adrenergic blockers

II. β adrenergic blockers

III. Adrenergic neuron blockers

They act by inhibition of

Release of Noradrenaline

Guanethidine

Storage of Noradrenaline

Reserpine

Synthesis of Noradrenaline

α methyl dopa

1. Guanethidine

Mechanism of action

1. inhibit NA release
2. inhibit NA uptake

Pharmacological actions

1. Decrease blood pressure
2. Does not antagonize exogenous catecholamines but it potentiates them

Therapeutic uses

1. Hypertension
2. Glaucoma

Side effects

1. Postural / orthostatic hypotension
2. impotence (failure of ejaculation)
3. Diarrhea
4. Nasal congestion

2. Reserpine

Mechanism of action

1. inhibits granular uptake (storage) of NA so, MAO can rapidly metabolize it in the cytoplasm that leads to depletion of NA
2. Reserpine causes depletion of stores of catecholamines and serotonin centrally (in brain) and peripherally (in organs)

Pharmacological actions

1. Centrally: ↓ NA in brain leads to sedation and tranquilizing actions
2. Peripherally: Hypotension

Therapeutic uses

1. Hypertension
2. Psychotic states

Side effects

1. Postural / orthostatic hypotension
2. Mental depression and suicidal attempts
3. Sedation
4. Nightmares

3. Alpha methyl dopa

Mechanism of action

1. inhibition of DOPA decarboxylase enzyme so prevent synthesis of NA → and produces α -methylnoradrenaline which is a false transmitter stored at the nerve ending instead of NA

2. α -methylnoradrenaline stimulates α_2 receptors in the brain → leading to decrease NA release and decrease sympathetic tone

Therapeutic uses

Hypertension
(Methyldopa is safe during pregnancy)